REMARKS

After entry of the present amendment, Claims 1-8, 10, 12, 14-22, 63-70 are pending. Claims 1 and 69 are hereby amended. New Claim 70 has been added. Support for the claim amendments and new claim can be found in the originally filed claims and throughout the Specification, for example, at page 4, line 25 – page 5, line 6; page 5, lines 22 – 24; and page 40, lines 9 – 18.

ARGUMENTS

I. Claim rejections under 35 U.S.C. §112, first paragraph

The Examiner has rejected Claims 1-8, 10, 12, 14-22, and 63-69 under 35 U.S.C. §112, first paragraph. Final Office Action at page 2. In rejecting the claims, the Examiner asserts that "[t]here is no support for the limitation, 'removing ammonium sulphate from extraliposomal hydration medium by dialysis, ultra filtration or column chromatography' using a sucrose-histidine buffer solution." *Id.* Applicants respectfully disagree, but have amended Claim 1 solely in order to facilitate prosecution. Accordingly, Applicants submit that the pending claim rejection is hereby rendered moot.

Without being limited, support for the phrase "removing ammonium sulphate from extraliposomal hydration medium by dialysis using a sucrose-histidine buffer solution" may be found in the Specification, for example, at page 4, line 25 – page 5, line 6 and page 40, lines 12 – 18. Specifically, as set forth in the Specification at page 40, lines 12 – 18:

> "The suspension of the sized liposomes was dialyzed against a histidine buffer. A tangential flow filtration system was used for the dialysis. The dialysis was continued till extra liposomal ammonium sulfate was removed. The absence of ammonium sulfate in extra liposomal media was confirmed using Nesseler reagent. The histidine hydrochloride solution used in the dialysis and drug loading (below) was as follows: 170.0 gm of sucrose, 3.40 gm of histidine HCl, 1.7 Liters of water, and sodium hydroxide at a quantity sufficient to adjust pH to 6.0 to 6.5."

As set forth above, the claims are supported by the Specification and therefore satisfy the written description requirement under 35 U.S.C. §112, first paragraph. Accordingly, Applicants respectfully request withdrawal of this ground of rejection.

2. Claim rejections under 35 U.S.C. §112, second paragraph

The Examiner has rejected Claim 69 under 35 U.S.C. §112, second paragraph, as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Final Office Action at page 3.

In rejecting the claims, the Examiner asserts that it is unclear how one can replace ammonium sulfate with a sucrose-histidine solution in an ultra-filtration process. Final Office Action at page 3. Applicants respectfully disagree, but have amended Claim 1 solely in order to facilitate prosecution by removing the term "ultrafiltration." Accordingly, Applicants submit that the pending claim rejection is hereby rendered moot.

Moreover, in rejecting the claims, the Examiner asserts that "[i]t is unclear as to what applicant intends to convey by at least 25 times longer than conventional ***non-liposomal*** formulations when tested in Swiss albino mice at equivalent doses." Office Action at page 3. (Emphasis in original). Applicants disagree.

Applicants respectfully submit that the scope of Claim 69 is clear. That is, the phrase "long circulating non-pegylated liposomes have a blood circulation half life of at least 25 times longer than conventional non-liposomal formulations when tested in Swiss albino mice at equivalent doses" is clearly supported and defined by the Specification. Specification, for example, at page 5, lines 28-30. As set forth in M.P.E.P. § 2173.04, "[b]readth of a claim is not to be equated with indefiniteness. *In re Miller*, 441 F.2d 689, 169 USPQ 597 (CCPA 1971). If the scope of the subject matter embraced by the claims is clear, and if applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, then the claims comply with 35 U.S.C. 112, second paragraph." Accordingly, since the scope of claim 69 is clear and unambiguously defined by the Specification, claim 69 satisfies 35 U.S.C. 112, second paragraph.

3. Claim rejections under 35 U.S.C. §103(a)

Claims 1-8, 10, 12, 14-22, and 63-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over the following references in various combinations: Kirpotin (U.S. Patent No. 6,110,491) in view of Wong (U.S. Patent Application No. 2005/0025822), Mammarella (U.S. Patent Application No. 2006/0078605) individually or in combination further with Papahadjopoulos (U.S. Patent No. 4,235,871); Hong (Clinical Cancer Research, 1999); Janoff (U.S. Patent No. 4,880,635); Radhakrishnan (U.S. Patent No. 5,192,528) or Uchiyama (International J. of Pharm., 1995); Forssen

(U.S. Patent No. 5,714,163). Applicants disagree with the Examiner's rejection under 35 U.S.C. §103(a).

At the outset, Applicants respectfully assert that neither Wong nor Mammarella are proper prior art. The instant application is entitled to a priority date of at least December 31, 2002. A proper priority claim was made to Provisional Patent Application No. 11.01/Mum/02, filed on December 31, 2002, and this claim has been previously perfected by the submission of a Certified English language copy of Provisional Patent Application No. 11.01/Mum/02, submitted to the USPTO on April 18, 2007.

Wong was filed on May 24, 2004 and claims priority to U.S. Provisional Application No. 60/475,080, filed on May 30, 2003. Therefore, at best, Wong is entitled to priority date of May 30, 2003. This date is after the effective priority date of the instant application and, as such, Wong can not be applied as prior art under 35 U.S.C. §103(a).

Mammarella is not proper prior art against the claims. Mammarella has a publication date of April 16, 2006 and claims priority to PCT/BR03/00123, filed on August 23, 2003. This date is after the effective priority date of the instant application and, as such, Mammarella can not be applied as prior art under 35 U.S.C. §103(a). Accordingly, neither Wong nor Mammarella are proper prior art under 35 U.S.C. §103(a). As such, Applicants respectfully request that the Examiner withdraw the current rejection.

As set forth in the Response submitted on July 2, 2009, none of the cited references, alone or in combination teach or suggest two of the claim elements: 1) an aqueous hydration buffer comprising ammonium sulfate and sucrose; and 2) removing ammonium sulphate from extraliposomal hydration medium using a sucrose-histidine buffer solution.

"an aqueous hydration buffer comprising ammonium sulfate and sucrose"

The claims include an aqueous hydration buffer comprising ammonium sulfate and sucrose. Not one of the references cited by the Examiner teach or fairly suggest this element. The Examiner's primary reference, Kirpotin, does not teach an aqueous hydration buffer comprising ammonium sulfate and sucrose. Kirpotin actually teaches away from using ammonium sulfate and sucrose because when Kirpotin used ammonium sulfate alone, his pegylated liposomes had the lowest performance. Kirpotin found that ammonium sulfate gives a poor precipitation and thus poor loading efficiency but found that polyacrylate type precipitating agents in the hydration medium provided a better loading efficiency. One skilled in the art after reading Kirpotin would thus not be motivated to take ammonium sulfate,

which did not work well and combine it with sucrose when Kirpotin leads the reader to abandon the use of ammonium sulfate altogether and instead use a polymer such as polyacrylate. Further, Kirpotin is directed to a loading mechanism and this mechanism involves forming a precipitate with a polymer whereas the ammonium sulfate and sucrose solution used in the present invention is for forming the liposomes. There is thus no teaching or suggestion by Kirpotin to use hydration buffer comprising ammonium sulfate and sucrose, let alone combine it with any other reference teaching ammonium sulfate or sucrose.

Wong and Mammarella did not use ammonium sulfate and sucrose and in addition, these references are not proper prior art as they are after the priority date of the present application.

In addition, Papahadjopoulos, Hong, Radhakrishnan, and Uchiyama do not use ammonium sulfate and sucrose in the hydration buffer either.

Further, Forssen does not teach an aqueous hydration buffer comprising ammonium sulfate and sucrose. Forssen has a buffer with ammonium salt or sucrose but does not teach a hydration buffer with ammonium sulfate and sucrose.

Emmanuel also does not teach an aqueous hydration buffer comprising ammonium sulfate and sucrose. Emmanuel's hydration buffer only has ammonium sulfate. Sucrose is used for tonicity in the composition but sucrose and ammonium sulfate are not used as a hydration buffer as required by the claims.

Thus, none of the cited art teaches or suggests the claim element of an aqueous hydration media comprising ammonium sulfate and sucrose. For this reason alone, all of the 35 U.S.C. § 103(a) rejections should be withdrawn. In addition, as shown below, none of the cited references teach another claim element: "removing extraliposomal hydration media using a sucrose-histidine buffer solution."

"removing extraliposomal hydration media using a sucrose-histidine buffer solution"

The cited references do not teach another claim element – namely removing extraliposomal hydration media using a sucrose-histidine buffer solution.

Neither Kirpotin, Forssen, Janoff, Papahadjopoulos, Hong, Radhakrishan, Uchiyama, Emmanuel, Mammarella or Wong teach or suggest removing extraliposomal hydration media using a sucrose-histidine buffer solution, as included by the claims. In addition, as mentioned above, Mammarella and Wong are not proper prior art references. Although Papahadjopoulos mentions

histidine in a hydration buffer, there is no teaching or suggestion to use a sucrose-histidine buffer solution for removing extraliposomal hydration media. Emmanuel mentions histidine for pH control but does not teach or suggest a sucrose-histidine buffer solution for removing extraliposomal hydration media.

Thus, none of the cited art teaches or suggests the claim element of removing extraliposomal hydration media using a sucrose-histidine buffer solution. For this reason alone, all of the 35 U.S.C. § 103(a) rejections should be withdrawn. In addition, as shown above, none of the cited references also teach another claim element of the hydration media comprising ammonium sulfate and sucrose. Therefore there are at least two claim elements not taught or suggested by any of the references alone or in combinations. As such, the 35 U.S.C. § 103(a) rejections are improper and should be withdrawn. Applicants request withdrawal of these grounds of rejection and allowance of the pending claims.

CONCLUSION

Thus, applicants have shown that none of the cited references actually teach each and every element of the claim nor do they suggest these elements, and the combination of every cited reference does not teach or suggest all of the claim elements. Accordingly, applicants request withdrawal of all of the rejection and request allowance of the present claims. The Commissioner is hereby authorized to charge any fee or credit any overpayment to Deposit Account No: 50-4254.

Respectfully Submitted,

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